

REMARKS

A. The Status of the Claims and the Amendments

By the present amendment, claim 105 has been amended to claim the invention with greater specificity, particularity, and accuracy. No new matter have been introduced in the amendments to the pending claims or with the new claims.

More specifically, claim 105 now recites "plurality of protein-halide vesicles" comprising a protein and where an organic halide is incorporated in the core of the vesicles. These limitations are disclosed in the originally filed application. See, e.g., page 16, lines 6-7 (protein used to formulate vesicles) and page 27, lines 17-18 (halide is incorporated in the core of the vesicles).

Upon entry of this amendment, claims 105-116 will be pending, of which claims 105-110 are currently under consideration, and claims 110-116 are currently withdrawn.

B. Rejections Under 35 U.S.C. § 102(b)

The Examiner mentioned rejections under 35 U.S.C. § 102(b) (page 4, line 15 through page 5, line 13 of the Final Office Action) over the references previously cited against claim 1, i.e., the following references: Stanko, Harth, Cella, Grimm, Pader '418, Pader '362, Kraus, Spero, Higuchi, Jederstrom, Cook '126, Cook '923, Cook '209, Witkowski, Golub, Gwaltney, Gristina, Sarzaud, and Love.

None of the nineteen references can qualify as a 102(b) reference, because none teaches all the elements and limitations recited in claim 105. In particular, claim 105 recites a method of delivery of vesicles which requires using one of specifically enumerated organic halides further recited in claim 105. None of the references describe nor even suggest making such vesicles.

As discussed in great detail in the previous response, Stanko fails to teach or suggest using any protein, as required by claim 105. Stanko only described the delivery of isoproterenol, which is not a protein.

Each of Harth, Cella, Grimm, Pader '418 and Pader '362, teaches using only chloroform and no other organic halide. None of the halides recited in claim 105 is used in any of Harth, Cella, Grimm, Pader '418 and Pader '362.

As to the next two references, Kraus and Spero, like Stanko discussed above, neither Kraus nor Spero describes or suggests the use of any protein.

Higuchi discloses the use of certain halogenated products (such as trichloro- and trifluoroethanol) for the delivery of proteins, but does not describe or suggests using any organic halide recited in claim 105.

Next seven references teach the delivery of 7-(β -hydroxypropyl)theophylline (Jederstrom) or steroids (each of Cook '126, Cook '923, and Cook '209), or antiviral agents (Witkowski, Golub) or anti-inflammatory compounds (Gwaltney). There is nothing in Jederstrom or any of the three Cook references, or in Witkowski, in Golub, or in Gwaltney teaching or suggesting the delivery of any protein, as required by claim 105. Neither theophylline, any steroid taught by Cook, any antiviral compound taught by Witkowski, any calcium-channel blocking agent of Golub, nor any antiviral and anti-inflammatory agent disclosed by Gwaltney is a protein.

The final three references teach the delivery of various biocompatible particles, such as opsonized zymosan, PMMA latex, and polystyrene (Gristina), or transdermal administration of various medications (Sarzuad), or asthma medications by inhalation (Love). Some of the products so delivered are polymers (e.g., in Gristina) but none is a protein and there is nothing in any of Gristina, Sarzuad, or Love describing or suggesting the use of any proteins to be delivered.

In view of the foregoing it is submitted that claim 105 is patentably distinguishable over all the cited references, and each of claims 106-110 depends on claim 105 and is considered patentable for at least the same reasons. Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. § 102(b) are respectfully requested.

C. Rejections Under 35 U.S.C. § 103(a)

Claims 105-110 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Harth, or Cella, or Grimm, or Pader '418, or Pader '362, or Higuchi, or a combination thereof, in view of Stanko, or Kraus, or Spero, or Jederstrom, or Cook '126, or Cook '923, or Cook '209, or Witkowski, or Golub, or Gwaltney, or Gristina, or Sarzaud, or Love, or a combination thereof (page 6, lines 3-7 of the Office Action). These rejections are respectfully traversed on the following grounds.

The KSR standard that has to be satisfied in order to make a valid rejection based on a *prima facie* case of obviousness was described in a response to a previous Office Action.

The Examiner has cited Harth, Cella, Grimm, Pader '418, Pader '362, and Higuchi as allegedly teaching the delivery of certain enzymes in combination with halides; however, none of the halides described is used in the present invention. Then Stanko, Kraus, Spero, Jederstrom, Cook '126, Cook '923, Cook '209, Witkowski, Golub, Gwaltney, Gristina, Sarzaud, and Love allegedly teach the delivery of certain compounds, none of which is a protein, in combination with various halides. The Examiner either modifies each of these references or combines them to arrive to what is claimed in claims 105-110 to make out the *prima facie* case of obviousness.

The Applicants respectfully disagree. As discussed previously each of Harth, Cella, Grimm, Pader '418, Pader '362, is directed to enzyme-containing toothpastes. There is nothing in these references indicating a delivery of any enzyme into any cell. Merely a contact of the enzyme with epithelial cells, which is disclosed, is clearly not nearly enough to achieve the delivery, as it is very clear to those skilled in the art. As the references themselves explicitly teach, the enzymes are used for different purposes, such as to dissolve dental tartar.

The Higuchi reference, it teaches administering of insulin, and possibly some other proteins. Higuchi also describes that fluorinated compounds are used in the delivery. However, there are no reasonable grounds to believe that there could conceivably be any motivation to modify Higuchi as suggested by the Examiner.

Claim 105 requires that the entire protein-halide composition be delivered into a cell, while in Higuchi the freons are used as propellants evaporating prior to any entry into a cell. Second, as to "promoters" described by Higuchi (trichloroethanol, trifluoroethanol), the instant claims do not recite such compounds. To modify the instant claims over Higuchi means to use such promoters so that the promoter-protein combination would penetrate a cell. There is absolutely no such motivation in Higuchi. And there is no indication that any delivery will be through a cell membrane, cell wall, and nuclear membrane, as claim 105 now requires.

It is, therefore, submitted that in a topical application described by Higuchi, the protein alone will enter a body. There is nothing in Higuchi indicative of any likelihood of intracellular penetration. Accordingly, it is the Applicants' position that Iguchi, alone or in combination with any other reference cannot be used to establish a *prima facie* case of obviousness, as it fails to satisfy the KSR test described above.

Turing now to Stanko, Kraus, Spero, Jederstrom, Cook '126, Cook '923, Cook '209, Witkowski, Golub, Gwaltney, Gristina, Sarzaud, and Love one can see that none of them describes delivery of any protein. The Examiner proposes to modify these references to extend the delivery methods to proteins. The Applicants respectfully point out that there is no motivation to do so, and even if these references were modified in such a way, they would still fail to teach or suggest all of the limitations of claim 105.

Stanko teaches delivery of isoproteronol using an alcohol and fluorinated hydrocarbons. The fact that this compound touches the epithelial cells is not enough to establish motivation. There is no indication that the compositions useful to deliver isoproteronol will be also useful for delivering much bulkier products such as proteins.

The same applies to Kraus, Spero, Jederstrom, and Sarzaud that disclose the delivery of various low molecular weight compounds in combination with halides. The fact that freon can be delivered in such a way provides no motivation to deliver a protein in a similar fashion, due to the great difference between the physical and chemical properties between such low molecular weight compounds and proteins. Each of the former group, is completely different from the latter in every respect; therefore the same delivery approach should not apply for both kinds of compounds.

The same lack of motivation applies to Cook, Love, Witkowski, Golub, and Gwaltney that disclose the delivery of steroids (the Cook references), corticosteroid beclomethasone dipropionate (Love), anti-viral medicine (Witkowski), or gallopamil or other calcium-channel blockers (Golub), or various anti-viral or anti-inflammatory agents (Gwaltney) in combination with halides. There is nothing at all in common between any of these compounds and any protein. All the compounds delivered according to the methods described in these references are completely different from proteins, chemically, physically, and in every other respect. There is nothing in these references or anywhere else which would suggest the same delivery approach for both.

Finally, Gristina teaches delivery of phagocytosable particles, such as of biodegradable particles, opsonized zymosan, PMMA latex, polystyrene, heat killed-BCG, and heat killed Staphylococcus epidermis, in combination with fluorinated hydrocarbons. Obviously, there is nothing common between these products ranging from synthetic polymer (PMMA) to bio materials, and proteins. The same rationale applies here as discussed above. Short of having a strong motivation to do so, one skilled in the art would not use the same delivery methods for these phagocytosable particles and for proteins. Gristina is not a reference providing such a motivation.

In view of the foregoing, it is submitted that claim 105 is patentably distinguishable over the references cited by the Examiner, or any combination thereof. Each of claims 106-110

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depends claim 105 and is patentably allowable for at least the same reason. Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, reconsideration and favorable action on all claims are respectfully requested. In the event any matters remain to be resolved, the Examiner is requested to contact the undersigned at the telephone number given below so that a prompt disposition of this application can be achieved.

The Commissioner is hereby authorized to charge \$405.00 as payment for the Request for Continued Examination fee to Deposit Account No. 07-1896. Additionally, the Commissioner is hereby authorized to charge any other fees that may be due in connection with the filing of this paper, or credit any overpayment to Deposit Account No. 07-1896, referencing the above-identified docket number.

Respectfully submitted,

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